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Uptake and discontinuation of integrase inhibitors (INSTIs) in a large cohort setting

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Abstract

Background

Despite increased INSTI use, limited large-scale, real-life data exists on INSTI uptake and discontinuation.

Setting

International multicohort collaboration.

Methods

RESPOND participants starting dolutegravir (DTG), elvitegravir (EVG) or raltegravir (RAL) after 1/1/2012 were included. Predictors of INSTI used were assessed using multinomial logistic regression. Kaplan Meier and Cox proportional hazards models describe time to and factors associated with discontinuation.

Results

Overall, 9702 persons were included; 5051 (52.1%) starting DTG, 1933 (19.9%) EVG, 2718 (28.0%) RAL. The likelihood of starting RAL or EVG versus DTG decreased over time and was higher in Eastern and Southern Europe compared to Western Europe.

At 6 months after initiation, 8.9% (95% CI 8.3%-9.5%) had discontinued the INSTI (6.4% DTG, 7.4% EVG, 14.0% RAL). The main reason for discontinuation was toxicity (44.2% DTG, 42.5% EVG, 17.3% RAL). Nervous system toxicity accounted for a higher proportion of toxicity discontinuations on DTG (31.8% DTG, 23.4% EVG, 6.6% RAL). Overall, treatment simplification was highest on RAL (2.7% DTG, 1.6% EVG, 19.8% RAL).

Factors associated with a higher discontinuation risk included increasing year of INSTI initiation, female gender, hepatitis C coinfection, and prior non-AIDS defining malignancies. Individuals in Southern and Eastern Europe were less likely to discontinue. Similar results were seen for discontinuations after 6 months.

Conclusion

Uptake of DTG versus EVG or RAL increased over time. Discontinuation within 6 months was mainly due to toxicity; nervous system toxicity was highest on DTG. Discontinuation was highest on RAL, mainly due to treatment simplification.

Keywords: HIV; integrase inhibitors; dolutegravir; raltegravir; elvitegravir; toxicity

Introduction

Integrase strand transfer inhibitors (INSTIs) are one of the latest antiretroviral drug classes to be approved for use as part of combination antiretroviral therapy (ART) regimens to control HIV[1]. Current HIV treatment guidelines recommend that initial ART regimens for adults include a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third agent consisting of an INSTI, boosted protease inhibitor (PI/b) or non-nucleoside reverse transcriptase inhibitor (NNRTI)[2,3]. There are currently four INSTIs approved by the European Medicines Agency. Raltegravir (RAL)[4,5] was the first to be approved in 2008, followed by elvitegravir (EVG)[6,7] in 2013, dolutegravir (DTG)[8–11] in 2014, and bictegravir (BIC)[12,13] in 2018.

Commonly reported adverse effects (AEs) associated with INSTIs include headache, nausea, and sleep disturbances[14]. Additionally, cobicistat boosted EVG (EVG/c) and DTG may cause inhibition of renal tubular secretion of creatinine, causing an artefactual increase in creatinine plasma levels not reflective of a declining renal function[10,15,16]. Whilst the frequency of drug-drug interactions on INSTIs as a class is relatively low, it is higher on EVG, due to the need for a pharmacokinetic enhancer[2] .

Several randomised controlled trials (RCTs) have demonstrated good virological efficacy, fewer AEs, and lower rates of discontinuation with INSTIs compared to NNRTIs[6,10,17–20], and PI/b[7,15,21–24]. These results have been confirmed in small observational studies[14,25,26]. However, despite the growing evidence, limited data exist on the choice of INSTIs and discontinuation of INSTIs in larger and more heterogeneous real-world settings. Access to individual INSTIs and reasons for discontinuation of INSTIs may differ among countries and subgroups, such as males versus females. Additionally, due to their presumed favourable safety profile, it is likely that a higher proportion of those with existing comorbidities are receiving INSTIs.

We aimed to describe the characteristics of those initiating INSTIs for the first time in heterogeneous real-world settings across Europe and Australia. We also aimed to describe time to and reasons for discontinuation of initial INSTI regimens and describe the characteristics of those discontinuing INSTIs.

Methods

Study Design and Participants

The International Cohort Consortium of Infectious Diseases (RESPOND) is a collaboration of 14 observational cohort studies across Europe and Australia, including 26,415 individuals living with HIV-1. Demographic and clinical data were retrospectively collected back to 2012 and are prospectively collected from 2017.

Standardised data including information on demographics, HIV-related factors, ART start and stop dates, and reason for discontinuation, coinfections, comorbidities and biomarkers are collected at time of enrolment and annually thereafter as part of routine clinical care (details at https://www.chip.dk/Studies/RESPOND). All cohorts used the HIV Cohorts Data Exchange Protocol (HICDEP) for data collection (details at https://hicdep.org/).

Individuals were included in this analysis if they had started DTG, EVG/c or RAL (persons were not necessarily ART-naïve) after the latest of local cohort enrolment and 1st January 2012, were aged ≥ 16, and had a CD4 cell count and viral load (VL) measurement prior to or within 6 months after starting an INSTI. Individuals were excluded from the analysis if they had missing information on gender. Final follow-up in our study was the last clinic visit prior to 2018.

Definition of outcomes

The first outcome was defined as uptake of DTG, EVG/c, or RAL. Individuals starting more than one INSTI during follow-up were included in the first INSTI group they were exposed to.

The second outcome was defined as discontinuation of first INSTI regimen during follow-up, provided individuals had been on the INSTI for at least 7 days (<1% of discontinuations occurred within 7 days of starting INSTIs). Discontinuation was not counted if an individual switched from a single tablet regimen (STR) to its individual components or vice versa, while remaining on the same INSTI, provided there was no interruption between treatments, nor if the backbone changed, provided the INSTI component remained the same. Discontinuations were split into discontinuation within 6 months and after 6 months of INSTI initiation.

Definition of potential predictors

The following variables, defined prior to or at INSTI initiation, were considered as potential predictors: year of starting INSTI, age, gender, HIV risk category, ethnicity, CD4 cell count nadir, CD4 cell count at INSTI initiation, smoking status, ART experience and viral suppression status, viral hepatitis B and C status (HBV/HCV), hypertension, diabetes, AIDS defining event (ADE), non-AIDS defining malignancy (NADM), end stage liver disease, cardiovascular disease (CVD), fracture, chronic kidney disease, and geographical region. For the INSTI discontinuation models, INSTI type was fitted as a potential predictor.

CD4 cell count at INSTI initiation was taken as the most recent CD4 count before initiation. If no CD4 count was measured, the first measurement within 6 months after INSTI start was used for both CD4 at INSTI initiation and CD4 cell nadir.

Geographical region was categorised as in previous EuroSIDA analyses[27]. Due to low numbers, Australia was combined with Northern Europe in the analysis models, and Eastern Central Europe was combined with Eastern Europe.

Statistical methods

Risk ratios using multinomial logistic regression were used to assess associations between baseline characteristics and the likelihood of starting RAL compared to DTG and of starting EVG/c compared to DTG. Baseline was defined as date of INSTI start. DTG was chosen as the reference category because it was the largest group and most recently approved INSTI. Each variable was included in univariable models and then all variables were fitted simultaneously in a multivariable model.

Results of the multivariable model were compared between ART-naïve, ART-experienced with VL<400 copies/mL and ART-experienced with VL≥400 copies/mL. Prespecified subgroup analyses were performed by fitting an interaction term between age and each of gender, HBV/HCV status, and each comorbidity listed above.

Discontinuation of DTG, EVG/c, and RAL was summarised using Kaplan Meier (KM) estimates. Reasons for discontinuation of each INSTI were summarised. For each drug discontinuation one underlying reason was provided by the participating cohort at the clinician's judgement. Reasons reported were grouped into treatment failure, toxicity, patient/physician choice (without further details), treatment simplification, other, and unknown. Discontinuations due to toxicity were further broken down into the individual reasons provided. Patient/physician choice was included as a marker of potential toxicity, as in previous EuroSIDA studies [28].

Cox proportional hazards models were used to assess factors associated with time to discontinuation, including all variables listed above. Each variable was included in univariable models and then all were fitted simultaneously in a multivariable model. Individuals were censored at final follow up, defined as last clinical visit, drop out date as defined by the cohort, or date of death.

Prespecified subgroup analyses were performed between INSTI type and each of gender, age, HIV risk group, HBV/HCV status, and each comorbidity listed above.

In all analysis models, an unknown category was used to account for missing data for categorical variables. As some cohorts were missing data on specific comorbidities, we did not adjust for cohort in the primary analysis. Sensitivity analyses were performed including cohort as an explanatory variable and excluding comorbidities. Additionally, the models were rerun using multiple imputation by chained equations to account for missing data with 10 imputations, including the same variables as those included in the primary analysis model. Results were combined using Rubin's rules.

Analyses were performed using Stata/SE 15.0. P-values are two sided and a p-value <0.05 was defined as statistically significant.

Results

Overall, 10,366 participants in RESPOND started an INSTI and of these, 9,702 (93.6%) were included in the analysis. Reasons for exclusion from the analysis are presented in supplementary Figure 1, http://links.lww.com/QAI/B408. Of those included, 5,051 (52.1%) started DTG, 1,933 (19.9%) started EVG/c and 2,718 (28.0%) started RAL. Of those on DTG and EVG/c, 35.1% and 88.4% were on STRs, respectively. The most commonly used backbone for DTG was abacavir (ABC) and lamivudine (3TC) (52.0%) and for EVG/c and RAL tenofovir disoproxil fumarate (TDF) with emtricitabine (FTC) (63.4% and 49.2%, respectively).

Baseline demographic and clinical characteristics are presented in Table 1. The majority of INSTI users were male, of white ethnicity and ART-experienced with a suppressed VL. The proportion who were ART-naïve was highest on EVG/c (30.4% on EVG/c vs 20.5% on RAL, 23.5% on DTG, p<0.001). There was a high incidence of prior ADEs (21.0% on DTG, 28.3% on RAL, 13.2% on EVG/c, p<0.001) and comorbidities, including hypertension, diabetes, and prior CVD (proportion with at least one comorbidity: 37.6% on DTG, 33.1% on RAL, 27.7% on EVG/c, p<0.001).

Uptake of INSTIs

Results from the univariable and multivariable multinomial logistic regression models are presented in supplementary Table 1, http://links.lww.com/QAI/B408 and Table 2, http://links.lww.com/QAI/B408, respectively. After adjustment, the likelihood of starting RAL or EVG/c compared to DTG decreased over time. Participants in Eastern and Southern Europe were more likely to start RAL or EVG/c compared to those in Western Europe. Increasing age at INSTI initiation was associated with an increased likelihood of starting RAL but a decreased likelihood of starting EVG/c. Female gender was also associated with a decreased likelihood of starting EVG/c. The likelihood of starting RAL was higher for participants who were ART-naïve or ART-experienced with ongoing viremia compared to those who were ART-experienced with a suppressed VL. In general, participants with comorbidities were more likely to start RAL but less likely to start EVG/c compared to DTG (Table 2). Adjusting additionally for the nucleoside backbone did not change our findings, except HBV coinfection, which was no longer associated with choice of INSTI.

We found a significant interaction between age and gender (p-value for interaction <0.001) for RAL vs DTG, showing that females were more likely to start RAL compared to men in younger age groups but were less likely to start RAL in older age groups (supplementary Figure 2, http://links.lww.com/QAI/B408). Other prespecified subgroup analyses were non-significant. Results were stratified by ART experience at baseline with similar findings. We repeated analyses adjusting for cohort instead of comorbidities with similar results. Multiple imputation to account for missing data also showed similar results (data not shown). As a post hoc analysis, we repeated analyses only including those starting an INSTI from 2015 (when DTG, EVG/c and RAL were available) and found similar results.

Discontinuation of INSTIs

Median follow-up time was longest on RAL (33.4 months IQR [16.7-48.3]), compared to EVG/c (17.7 [7.6-31.7]) and DTG (17.1 [8.5-26.2]). During follow up, 2,105 (21.7%) persons discontinued an INSTI; 619 (12.3%) discontinued DTG, 341 (17.6%) discontinued EVG/c, and 1,145 (42.1%) discontinued RAL. Amongst those discontinuing, median time to discontinuation was 6.3 months [2.7-14.0] on DTG, 8.9 [3.2-18.4] on EVG/c, 12.2 [4.4-24.0] on RAL.

KM plots of discontinuation, overall and by ART-experience are shown in Figure 1. The overall KM estimate of discontinuation at 6 months after INSTI start was 8.9% (95% CI: 8.3-9.5) and highest on RAL (14.0% [12.7-15.4] vs. 6.4% [5.7-7.2] on DTG, 7.4% [6.3-8.8] on EVG/c; $p<0.001$), and this was consistent between ART-naïve, ART-experienced with VL<400 copies/mL and ART-experienced with VL≥400 copies/mL. Overall, the KM estimates at 1 and 2 years were 10.0% [9.1-10.9] and 15.4% [14.2-16.7] for DTG, 13.1% [11.5-14.9] and 22.0% [19.7-24.5] for EVG/c, 22.6% [21.0-24.3] and 36.7% [34.7-38.7] for RAL. Discontinuation of RAL was highest in 2014 and 2015 when DTG and EVG/c were both approved.

Reasons for discontinuation overall, within 6 months after INSTI start, and after 6 months after INSTI start are presented in Figure 2a. Of all discontinuations by 6 months, the most commonly reported reason for discontinuation was toxicity (31.4% overall), followed by patient/physician choice (24.6% overall). Reasons for discontinuation were similar for DTG and EVG/c, with toxicity accounting for nearly half of all discontinuations in these groups (44.2% and 42.5% respectively). Conversely, of all discontinuations on RAL, the main reason reported was patient/physician choice (28.6%). Discontinuations for treatment simplification accounted for a considerably higher proportion of discontinuations on RAL compared to DTG or EVG/c (19.8% on RAL, 2.7% on DTG, 1.6% on EVG/c, $p<0.001$). We also compared reasons for discontinuation between males and females and found similar results.

Discontinuations due to toxicity were further broken down and compared between INSTI types (Figure 2b). Overall 439 persons discontinued an INSTI due to toxicity within 6 months after INSTI initiation. Nervous system toxicity accounted for a higher proportion of toxicity discontinuations on DTG (31.8% on DTG, 23.4% on EVG/c, 6.6% on RAL, $p<0.001$).

Overall 1,322 (13.6%) persons discontinued an INSTI more than 6 months after INSTI initiation: 327 (6.5%) on DTG, 214 (11.1%) on EVG/c, 781 (28.7%) on RAL. Of those, the most commonly reported reason was patient/physician choice, and this was reported for a similar proportion across all INSTIs (26.0%, 20.6%, 25.9% on DTG, EVG/c, and RAL, respectively, p=0.50). Toxicity remained the most common reason for discontinuation of DTG (29.7%) and EVG/c (22.4%), and treatment simplification was the most common reason on RAL (31.1%).

Factors associated with discontinuation within the first 6 months are presented in Figure 3. The adjusted risk of discontinuation was higher for RAL (hazard ratio [HR] 3.03, 95% CI [2.47-3.70]) and EVG/c (1.37 [1.10-1.69]) compared to DTG. Individuals who started an INSTI later were more likely to discontinue (1.11 per year later [1.04-1.18]), as were females (1.28 [1.06-1.55]), those with uncontrolled viremia compared to a suppressed VL in ART-experienced persons (1.38 [1.08-1.75]), and those with HCV (1.32 [1.06-1.66]) or prior NADM (1.55 [1.13-2.12]). Conversely, those in Southern (0.58 [0.43-0.78]) and Eastern Europe (0.31 [0.20-0.50]) were less likely to discontinue compared to those in Western Europe. Full results from the univariable and multivariable Cox regression models are presented in supplementary Table 2, http://links.lww.com/QAI/B408. Similar results were seen for discontinuations greater than 6 months after INSTI initiation (data not shown). As post hoc analyses, we additionally adjusted for BMI in the multivariable model, reran analyses including those starting an INSTI from 2015, and looked at predictors of INSTI discontinuation due to toxicity only; all showed similar results.

We found no evidence that the association between risk of discontinuation by 6 months and INSTI type differed according to ART-experience (p-value for interaction 0.51). Prespecified subgroup analyses showed a significant interaction between INSTI type and age group, shown in supplementary Figure 3, http://links.lww.com/QAI/B408 (p-value for interaction 0.001). Across all age groups, the risk of discontinuation was higher on RAL than on DTG; however, the difference between RAL and DTG decreased slightly in older age groups. There was an increased risk of discontinuation of EVG/c compared to DTG in the oldest age group (≥50 years); however, there was no difference in the risk in lower age groups.

Discussion

To the best of our knowledge, this is one of the first, large-scale studies investigating uptake and discontinuation of INSTIs in real-world settings across Europe and Australia. Despite being recommended as first line therapy in HIV treatment guidelines, scarce data exist on the choice of INSTIs used in real-world settings and data on INSTI discontinuation is typically limited to RCTs and smaller, national observational studies. This analysis of almost 10,000 persons starting an INSTI found that as the year of INSTI start increased, the likelihood of starting RAL or EVG/c decreased compared to DTG, with the greatest decline for RAL. Discontinuation was highest on RAL, mainly due to treatment simplification. Moreover, the proportion of individuals discontinuing due to toxicity was highest on DTG, although this proportion was low across all INSTIs.

Subgroup analyses of INSTI uptake showed that females were more likely to start RAL compared to males in lower age groups but were less likely to start RAL in older age groups. This may partly be because RAL is recommended in treatment guidelines for pregnant women (or women wishing to conceive), in particular those starting follow-up late or whose VL is not fully suppressed at the third trimester[2,29]. In older age groups, treatment simplification may be a higher priority for menopausal women; therefore, regimens containing DTG are likely to be favoured over RAL.

Furthermore, our analysis showed that those with HBV coinfection were more likely to start RAL or EVG/c, and those with prior CVD were also more likely to start RAL compared to DTG. Treatment guidelines recommend using a TDF or tenofovir alafenamide containing regimen in HBV coinfected individuals[2,30,31]. After adjustment for NRTI backbone the association between HBV and choice of INSTI was no longer significant, suggesting the backbone was likely driving this treatment choice rather than the INSTI. ABC has been associated with an increased risk of CVD and is commonly prescribed with DTG[32]. However, after adjusting for backbone, the association between CVD and the likelihood of starting RAL remained highly significant suggesting this decision was not driven by ABC.

During follow up, the risk of discontinuation was significantly higher on RAL compared to DTG or EVG/c, mainly due to treatment simplification. We found the rate of discontinuation on RAL was higher than reported in previous studies[5,14,25]. This is likely because the cut off for follow up in our study was the end of 2017, which was later than other studies and therefore reflects the increasing availability of newer INSTIs. For all INSTIs, the risk of discontinuation increased with later year of INSTI start, which may be related to the growing availability of post-marketing information on AEs associated with INSTIs and greater availability of treatment options[2,3,14,33–36]. Additionally, the risk of discontinuation was up to 3 times higher in Western Europe compared to other European regions, which may reflect the wider range of available treatment options in Western Europe[37].

The risk of INSTI discontinuation was also higher for females compared to males. This is in line with studies carried out by Hoffman et al.[38] and Llibre et al.[39], who reported an increased risk among females of DTG discontinuation and INSTI discontinuation due to AEs, respectively. Studies have suggested that the higher rates of AEs in females are due to a lower BMI leading to higher drug exposure[38,40]; however, after adjusting for BMI, there remained a significantly higher risk of discontinuation for females. Additionally, we found similar rates of discontinuation due to toxicity for females and males (32% and 31% of discontinuations, respectively). Our results suggest that further research is needed on the safety of INSTIs in females, who are often underrepresented in HIV research. Finally, INSTI users in older age groups were more likely to discontinue EVG/c compared to DTG, likely due to the increased frequency of drug interactions on EVG/c.

The most common reasons for INSTI discontinuation within 6 months after INSTI start were patient/physician choice and toxicity. Of those starting an INSTI, the proportion discontinuing within 6 months due to toxicity was relatively low on all INSTIs (3.9% DTG, 4.0% EVG/c, 6.1% RAL). This is an important and reassuring real-world finding showing that toxicities are not leading to high rates of INSTI discontinuation. The most common individual toxicity was from the nervous system for DTG and EVG/c and from the abdomen/gastrointestinal tract for RAL. This is in line with several observational studies that have reported higher rates of DTG discontinuation due to neuropsychiatric

AEs compared to other INSTIs[14,25,38,39,41–43]. As is the case with several recent observational studies and case reports[38,39,41–46], our results show a higher rate of discontinuation due to toxicity than reported in RCTs, especially on DTG. This likely reflects the selected population participating in RCTs and reflects the need for further investigation. Beyond 6 months after INSTI initiation, the most common toxicity for EVG/c was renal, likely attributable to the coformulation with TDF in the STR TDF/FTC/EVC/c and the increase in creatinine caused by cobicistat[47].

Our study has several limitations. Persons enrolled in RESPOND were not randomly selected as we pre-specified the minimum number of participants on INSTIs to be included in the cohort collaboration, and it is not possible to rule out confounding by indication or to fully adjust for all factors associated with choice and discontinuation of INSTIs. As is common with observational studies, there is a relatively high proportion of missing data, particularly for comorbidities. However, sensitivity analyses using multiple imputation to account for missing data showed similar results. Follow up for DTG in particular, may still be limited as the data cut-off for this analysis was the end of 2017. The reasons for discontinuation of INSTIs are those reported in patient notes and the proportion of unknown reasons, as well as the distribution of known reasons, differs considerably between cohorts. Only one reason was provided per discontinuation, and the reasons given are limited, for example, patient/physician choice may cover a wide range of reasons including concerns about toxicity, drug interactions, and adherence, however we did not have access to any further information. However, all cohorts used the HICDEP standard for reporting and have previously participated in the development of this standard. Finally, we did not collect data on non-antiretroviral treatment or pre-existing mental illness, which may affect the choice and discontinuation risk of INSTIs.

In conclusion, uptake of DTG compared to EVG/c or RAL has increased over calendar time, and more in Western Europe compared to other European regions. INSTI discontinuation was mainly due to toxicity in the first 6 months and patient/physician choice thereafter, but was low overall. Discontinuation was significantly higher for RAL, mainly due to treatment simplification, whilst discontinuation due to nervous system toxicities was highest on DTG. Our findings highlight the need for further research to better understand AEs on INSTIs.

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Author contributions: AM, LR, JDL developed the project proposal and statistical analysis plan. LG carried out the statistical analysis, wrote the first draft of the manuscript and subsequent drafts. AM, LR, LBM reviewed all versions of the manuscript and contributed to the interpretation of the data. GW, KG-P, AÖ, BN, CSte, AlC, AR, AnC, VS, MJ, CSti, CM, SDW, CN, AAC, CP, MS, J-CW, Ad'AM, ML, RP, NC, TT, HG, DT, JDL, LP reviewed the final draft of the manuscript and contributed to the interpretation of the data.

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References

1. U.S. Food and Drug Administration. Antiretroviral drugs used in the treatment of HIV infection.

2. EACS. *EACS Guidelines Version 9.1*.; 2018. http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf.

3. *World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection Recommendations for a Public Health Approach—Second Edition*.; 2016. doi:10.1097/00022744-199706000-00003

4. Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with Optimized Background Therapy for Resistant HIV-1 Infection. *N Engl J Med*. 2008;359(4):339-354. doi:10.1056/NEJMoa0708975

5. Eron JJ, Cooper DA, Steigbigel RT, et al. Efficacy and safety of raltegravir for treatment of HIV for 5 years in the BENCHMRK studies: Final results of two randomised, placebo-controlled trials. *Lancet Infect Dis*. 2013;13(7):587-596. doi:10.1016/S1473-3099(13)70093-8

6. Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet*. 2012;379(9835):2439-2448. doi:10.1016/S0140-6736(12)60917-9

7. DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for

initial treatment of HIV-1 infection: a randomised, double-. *Lancet*. 2012;379(9835):2429-2438. doi:https://doi.org/10.1016/S0140-6736(12)60918-0

8. Raffi F, Rachlis A, Stellbrink H-J, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet*. 2013;381(9868):735-743. doi:10.1016/S0140-6736(12)61853-4

9. Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. *Lancet*. 2013;382(9893):700-708. doi:10.1016/S0140-6736(13)61221-0

10. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection. *N Engl J Med*. 2013;369(19):1807-1818. doi:10.1056/nejmoa1215541

11. Eron JJ, Clotet B, Durant J, et al. Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. *J Infect Dis*. 2013;207(5):740-748. doi:10.1093/infdis/jis750

12. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380–1490): a randomised, double-blind, multicentre, phase 3, non-inferiori. *Lancet*. 2017;390:2073-2082. doi:10.1016/S0140-6736(17)32340-1

13. Gallant J, Lazzarin A, Mills A, et al. Bictegravir , emtricitabine , and tenofovir alafenamide versus dolutegravir , abacavir , and lamivudine for initial treatment of phase 3 , randomised controlled non-inferiority trial. *Lancet*. 2017;390:2063-2072. doi:10.1016/S0140-6736(17)32299-7

14. Peñafiel J, de Lazzari E, Padilla M, et al. Tolerability of integrase inhibitors in a real-life setting. *J Antimicrob Chemother*. 2017;72(6):1752-1759.

15. Arribas JR, Pialoux G, Gathe J, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results o. *Lancet Infect Dis*. 2014;14(7):581-589. doi:10.1016/S1473-3099(14)70782-0

16. Capetti A, Rizzardini G. Cobicistat: a new opportunity in the treatment of HIV disease? *Expert Opin Pharmacother*. 2014;15(9):1289-1298. doi:10.1517/14656566.2014.920008

17. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*. 2009;374(9692):796-806. doi:https://doi.org/10.1016/S0140-6736(09)60918-1

18. Nguyen A, Calmy A, Delhumeau C, et al. A randomized cross-over study to compare raltegravir and efavirenz (SWITCH-ER study). *Aids*. 2011;25(12):1481-1487. doi:10.1097/QAD.0b013e328348dab0

19. Rockstroh JK, Dejesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: Final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr*. 2013;63(1):77-85. doi:10.1097/QAI.0b013e31828ace69

20. Zolopa A, Sax PE, DeJesus E, et al. A Randomized Double-Blind Comparison of Coformulated Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Versus Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate for Initial Treatment of HIV-1 Infection: Analysis of Week 96 Results. *JAIDS J Acquir Immune Defic Syndr*. 2013;63(1).

21. Martinez E, Larrousse M, Llibre JM, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: The SPIRAL study. *Aids*. 2010;24(11):1697-1707. doi:10.1097/QAD.0b013e32833a608a

22. Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet*. 2014;383(9936):2222-2231. doi:10.1016/S0140-6736(14)60084-2

23. Gatell JM, Assoumou L, Moyle G, et al. Switching from a ritonavir-boosted protease inhibitor to a dolutegravir-based regimen for maintenance of HIV viral suppression in patients with high cardiovascular risk. *Aids*. 2017;31(18):2503-2514. doi:10.1097/QAD.0000000000001675

24. Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label. *Lancet HIV*. 2017;4(12):e536-e546. doi:10.1016/S2352-3018(17)30095-4

25. Elzi L, Erb S, Furrer H, et al. Adverse events of raltegravir and dolutegravir. *AIDS*. 2017;31(13):1853-1858. doi:10.1097/QAD.0000000000001590

26. Lepik KJ, Yip B, Ulloa AC, et al. Adverse drug reactions to integrase strand transfer inhibitors. *Aids*. 2018;32(7):903-912. doi:10.1097/QAD.0000000000001781

27. Laut K, Shepherd L, Radoi R, et al. Persistent disparities in antiretroviral treatment (ART) coverage and virological suppression across Europe, 2004 to 2015. *Eurosurveillance*. 2018;23(21):1-12. doi:10.2807/1560-7917.es.2018.23.21.1700382

28. Reekie J, Reiss P, Ledergerber B, et al. A comparison of the long-term durability of nevirapine, efavirenz and lopinavir in routine clinical practice in Europe: A EuroSIDA study. *HIV Med*. 2011;12(5):259-268. doi:10.1111/j.1468-1293.2010.00877.x

29. Blonk MI, Colbers APH, Hidalgo-Tenorio C, et al. Raltegravir in HIV-1–Infected Pregnant Women: Pharmacokinetics, Safety, and Efficacy. *Clin Infect Dis*. 2015;61(5):809-816.

30. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the international antiviral society-USA panel. *JAMA - J Am Med Assoc*. 2018;320(4):379-396. doi:10.1001/jama.2018.8431

31. British HIV Association. *British HIV Association Guidelines for the Treatment of HIV-1-Positive Adults with Antiretroviral Therapy 2015*. https://www.bhiva.org/file/RVYKzFwyxpgiI/treatment-guidelines-2016-interim-update.pdf.

32. The D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: A multi-cohort collaboration. *Lancet*. 2008;371(9622):1417-1426. doi:10.1016/S0140-6736(08)60423-7

33. Lepik KJ, Nohpal A, Yip B, et al. Adverse Drug Reactions Associated with Integrase Stand Transfer Inhibitors (INSTI) in Clinical Practice: Post-Marketing Experience with Raltegravir, Elvitegravir-Cobicistat and Dolutegravir. Toronto: IAS, Poster Abstract. 2015:Abstract TUPEB 256.

34. Viswanathan P, Baro E, Soon G, et al. Neuropsychiatric Adverse Events Associated With Integrase Strand Transfer Inhibitors: Center for Drug Evaluation and Research, Food and Drug Administration. 2016.

35. Teppler H, Brown DD, Leavitt RY, et al. Long-Term Safety from the Raltegravir Clinical Development Program. *Curr HIV Res*. 2011;9(1):40-53. doi:10.2174/157016211794582650

36. Manzardo C, Gatell J. Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate): a new paradigm for HIV-1 treatment. *AIDS Rev*. 2014;16(1):35-42.

37. Gokengin D, Oprea C, Begovac J, et al. HIV care in Central and Eastern Europe: How close are we to the target? *Int J Infect Dis*. 2018;70(2018):121-130. doi:10.1016/j.ijid.2018.03.007

38. Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. *HIV Med*. 2017;18(1):56-63. doi:10.1111/hiv.12468

39. Llibre JM, Montoliu A, Miró JM, et al. Discontinuation of dolutegravir, elvitegravir/cobicistat and raltegravir because of toxicity in a prospective cohort. *HIV Med*. 2019;(February 2017):13-16. doi:10.1111/hiv.12710

40. Ofotokun I, Chuck SK, Hitti JE. Antiretroviral pharmacokinetic profile: A review of sex differences. *Gend Med*. 2007;4(2):106-119. doi:10.1016/S1550-8579(07)80025-8

41. De Boer MGJ, Van Den Berk GEL, Van Holten N, et al. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. *Aids*. 2016;30(18):2831-2834. doi:10.1097/QAD.0000000000001279

42. Yombi JC. Dolutegravir neuropsychiatric adverse events: Specific drug effect or class effect. *AIDS Rev*. 2018;20(1):13-25. doi:10.24875/AIDSRev.M17000013

43. Menard A, Montagnac C, Solas C, et al. Neuropsychiatric adverse effects on dolutegravir: an emerging concern in Europe. *AIDS*. 2017;31(8):20-22. doi:10.1097/QAD.0000000000001457

44. Dube B, Benton T, Cruess D., Evans D. Neuropsychiatric manifestations of HIV infection and AIDS. *J Psychiatry Neurosci*. 2005;30(4):237-246.

45. Todd SEJ, Rafferty P, Walker E, et al. Early clinical experience of dolutegravir in an HIV cohort in a larger teaching hospital. *Int J STD AIDS*. 2017;28(11):1074-1081. doi:10.1177/0956462416688127

46. Bonfanti P, Madeddu G, Gulminetti R. Discontinuation of treatment and adverse events in an Italian cohort of patients on dolutegravir. *AIDS*. 2017;31:455-457.

47. Yombi JC, Pozniak A, Boffito M, et al. Antiretrovirals and the kidney in current clinical practice: Renal pharmacokinetics, alterations of renal function and renal toxicity. *Aids*. 2014;28(5):621-632. doi:10.1097/QAD.0000000000000103

48. Levey AS, Stevens LA, Schmid CH, et al. A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med*. 2013;150(9):604. doi:10.7326/0003-4819-150-9-200905050-00006

Figure Legends

Figure 1. Kaplan Meier plots of INSTI discontinuation: (a) overall; (b) in ART naïve individuals; (c) in ART experienced individuals with a viral load < 400 copies/mL; (d) in ART experienced individuals with a viral load ≥ 400 copies/mL

Figure 2 (a) Reasons for INSTI discontinuation; (b) Reasons for toxicity discontinuation; split by discontinuations ≤6 months and >6 months after INSTI start

Abbreviations: G-I – gastrointestinal; INSTI - integrase inhibitor
Discontinuation was not counted if the backbone changed or participants went from a single tablet regimen to individual components or vice versa, provided the INSTI component of the regimen remained the same
Other includes pregnancy, availability of more effective treatment, drug interaction, protocol change, regular treatment termination, end of empiric treatment, structured treatment interruption, study treatment commenced or completed.
Treatment failure includes virological failure, immunological failure, clinical progression, death; if the discontinuation reason was reported as other causes or unknown and the viral load at discontinuation (± 3 months) was greater than 400 copies/mL, this was counted as treatment failure.
Simplified treatment available includes simplified treatment available, treatment too complex;
Toxicity includes abnormal fat redistribution, concern of cardiovascular, hypersensitivity reaction, abdomen or gastrointestinal tract toxicity, nervous system toxicity, kidney toxicity, endocrine system toxicity, unspecified side effects;

Figure 3. Significant associations between baseline characteristics and INSTI discontinuation in the first 6 months after INSTI start

Table 1 Baseline characteristics of persons starting INSTIs in RESPOND, overall and by INSTI type - n (%) unless stated otherwise

		Overall		Dolutegravir		Raltegravir		Elvitegravir	
Total		9702	(100)	5051	(52.1)	2718	(28.0)	1933	(19.9)
Geographical region	Western Europe	5146	(53.0)	3025	(59.9)	1046	(38.5)	1075	(55.6)
	Southern Europe	2679	(27.6)	1318	(26.1)	728	(26.8)	633	(32.7)
	Northern Europe	1275	(13.1)	453	(9.0)	697	(25.6)	125	(6.5)
	Eastern Europe	490	(5.1)	216	(4.3)	176	(6.5)	98	(5.1)
	Eastern Central Europe	112	(1.2)	39	(0.8)	71	(2.6)	2	(0.1)
	Australia	119	(1.2)	52	(1.0)	40	(1.4)	27	(1.4)
Gender	Male	7322	(75.5)	3765	(74.5)	1998	(73.5)	1559	(80.7)
	Female	2378	(24.5)	1286	(25.5)	720	(26.5)	372	(19.2)
	Transgender	2	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)
Ethnic Origin*	White	6835	(82.6)	3691	(84.1)	1875	(81.2)	1269	(80.6)
	Black	1023	(12.4)	482	(11.0)	325	(14.1)	216	(13.7)
	Other	417	(5.0)	218	(5.0)	110	(4.8)	89	(5.7)
BMI*	<18.5	369	(5.4)	203	(5.2)	107	(7.0)	59	(4.2)
	18.5-<25	3887	(56.9)	2233	(57.2)	859	(56.0)	795	(56.9)
	≥25	2580	(37.7)	1469	(37.6)	569	(37.1)	542	(38.8)
Smoking status*	Never	2451	(40.8)	1402	(41.3)	548	(39.2)	501	(41.4)
	Current	2627	(43.8)	1488	(43.8)	607	(43.4)	532	(44.0)
	Previous	924	(15.4)	505	(14.9)	243	(17.7)	176	(14.6)
ART experience	Naïve	2330	(24.0)	1185	(23.5)	557	(20.5)	588	(30.4)
	Experienced, VL < 400 cps/mL	6541	(67.4)	3529	(69.9)	1798	(66.2)	1214	(62.8)
	Experienced, VL ≥ 400 cps/mL	831	(8.6)	337	(6.7)	363	(13.4)	131	(6.8)
HIV risk*	MSM	4356	(47.5)	2244	(47.0)	1121	(43.3)	991	(54.7)
	IDU	1396	(15.2)	735	(15.4)	460	(17.8)	201	(11.1)

	Heterosexual	3164	(34.5)	1669	(35.0)	911	(35.2)	584	(32.2)
	Other	256	(2.8)	124	(2.5)	95	(3.5)	37	(2.0)
Hepatitis C*,[1]		2193	(22.6)	1174	(23.2)	714	(26.3)	305	(15.8)
Hepatitis B*,[2]		439	(4.5)	189	(3.7)	148	(5.4)	102	(5.3)
Hypertension*,[4]		2264	(23.3)	1341	(26.5)	536	(19.7)	387	(20.0)
Diabetes*		763	(7.9)	398	(7.9)	242	(8.9)	123	(6.4)
Prior AIDS*		2085	(21.5)	1061	(21.0)	768	(28.3)	256	(13.2)
Prior NADM*		382	(3.9)	210	(4.2)	134	(4.9)	38	(2.0)
Prior ESLD*		83	(0.9)	37	(0.7)	40	(1.5)	6	(0.3)
Prior CVD*,[5]		344	(3.5)	152	(3.0)	149	(5.5)	43	(2.2)
Prior fracture*		458	(4.7)	261	(5.2)	125	(4.6)	72	(3.7)
Prior CKD*,[6]		359	(3.7)	196	(3.9)	125	(4.6)	38	(2.0)
Continuous variables, median (IQR)									
INSTI start date		Aug 2015	(Sept 2014, Jul 2016)	Jan 2016	(May 2015, Oct 2016)	Feb 2014	(Jan 2013, Apr 2015)	Dec 2015	(Oct 2014, Nov 2016)
Age, years		48	(39, 54)	48	(39, 55)	48	(41, 54)	45	(36, 53)
CD4 cell nadir, cells/mm³		213	(91, 350)	215	(93, 349)	179	(68, 311)	262	(138, 404)
CD4 at INSTI start, cells/mm³		552	(350, 761)	578	(369, 788)	507	(297, 714)	560	(386, 756)

Abbreviations: INSTI-integrase inhibitor; BMI-body mass index; ART-antiretroviral treatment; VL-viral load; MSM-men who have sex with men; IDU-intravenous drug user; NADM-non-AIDS defining malignancy; ESLD-end stage liver disease; CVD-cardiovascular disease; CKD-chronic kidney disease; IQR-interquartile range

Baseline is defined as the date of starting an INSTI

[1]HCV was defined by use of anti-HCV medication, a positive HCV antibody test, a positive HCV RNA qualitative test, HCV RNA-VL >615 IU/mL, and/or a positive genotype test.

[2]HBV was defined by a positive HBV surface antigen test and/or HBV RNA-VL >357 IU/mL.

[4]Hypertension was confirmed by use of anti-hypertensives at any time before INSTI start or if the most recent blood pressure measurement before INSTI start was higher than 140/90 mmHg.

[5]CVD was a centrally adjudicated event defined using a composite diagnosis of myocardial infarction, stroke or invasive cardiovascular procedure.

[6]CKD was confirmed if there were two consecutive measurements of estimated glomerular filtration rate (eGFR) $\leq$60 mL/min measured at least 3 months apart. eGFR was calculated using the CKD-EPI creatinine equation (47).

*Denominator for percentages is all participants with non-missing data.

Total unknown n (%): Ethnicity 1454 (14.8) BMI 2875 (29.2), Smoking status 3763 (38.3), HIV risk 535 (5.4), hepatitis C 1417 (14.4), hepatitis B 1672 (17.0), hypertension 2864 (29.1), diabetes 917 (9.3), prior AIDS 1143 (11.6), prior NADM 1995 (20.3), prior ESLD 5641 (57.4), prior CVD 2672 (27.2), prior fracture 2889 (29.4), prior CKD 1762 (17.9).

Table 2 Associations between characteristics at INSTI start and choice of INSTIs – multivariable analysis

			Raltegravir vs Dolutegravir			Elvitegravir vs Dolutegravir		
Variable	**Reference**	**Group**	**RR***	**(95% CI)**	**p-value**	**RR***	**(95% CI)**	**p-value**
INSTI start, per 1 calendar year later			0.25	(0.23, 0.26)	<0.001	0.81	(0.77, 0.85)	<0.001
Geographical region[1]	Western Europe	Southern Europe	3.00	(2.36, 3.81)	<0.001	1.23	(0.99, 1.52)	<0.001
		Northern Europe/ Australia	1.15	(0.86, 1.52)		0.68	(0.52, 0.90)	
		Eastern Europe	6.82	(5.07, 9.19)		1.36	(1.02, 1.81)	
Age, per 10-year increase			1.14	(1.06, 1.22)	<0.001	0.91	(0.86, 0.97)	0.002
Gender	Male	Female	0.98	(0.82, 1.17)	0.80	0.68	(0.58, 0.80)	<0.001
Ethnic origin†	White	Black	1.00	(0.77, 1.30)	0.99	1.24	(1.00, 1.54)	0.11
		Other	0.98	(0.68, 1.42)		1.14	(0.87, 1.50)	
Smoking status†	Never	Current	1.03	(0.85, 1.24)	0.82	1.10	(0.94, 1.29)	0.46
		Previous	1.08	(0.85, 1.38)		1.04	(0.84, 1.28)	
ART experience	Experienced, VL<400 cps/mL	Naive	1.29	(1.03, 1.63)	<0.001	0.99	(0.82, 1.19)	0.61
		Experienced, VL≥400 cps/mL	1.56	(1.22, 2.00)		1.12	(0.88, 1.41)	
HIV risk†	MSM	IDU	1.37	(1.06, 1.76)	0.004	1.01	(0.80, 1.28)	0.53
		Heterosexual	1.33	(1.10, 1.60)		1.10	(0.94, 1.29)	
		Other	1.69	(1.11, 2.57)		0.88	(0.59, 1.32)	
CD4 nadir, cells/mm^3	<200	200-349	0.97	(0.81, 1.16)	0.57	1.09	(0.94, 1.27)	0.70
		350-499	0.93	(0.73, 1.18)		1.07	(0.88, 1.31)	
		≥500	1.14	(0.85, 1.53)		1.06	(0.84, 1.35)	
CD4 at INSTI start, cells/mm^3	<200	200-349	0.92	(0.70, 1.21)	0.16	1.75	(1.34, 2.27)	<0.001
		350-499	0.84	(0.64, 1.10)		1.88	(1.45, 2.44)	
		≥500	0.76	(0.58, 0.99)		1.66	(1.27, 2.17)	
Hepatitis C†	No	Yes	1.39	(1.13, 1.72)	0.002	0.80	(0.66, 0.98)	0.03

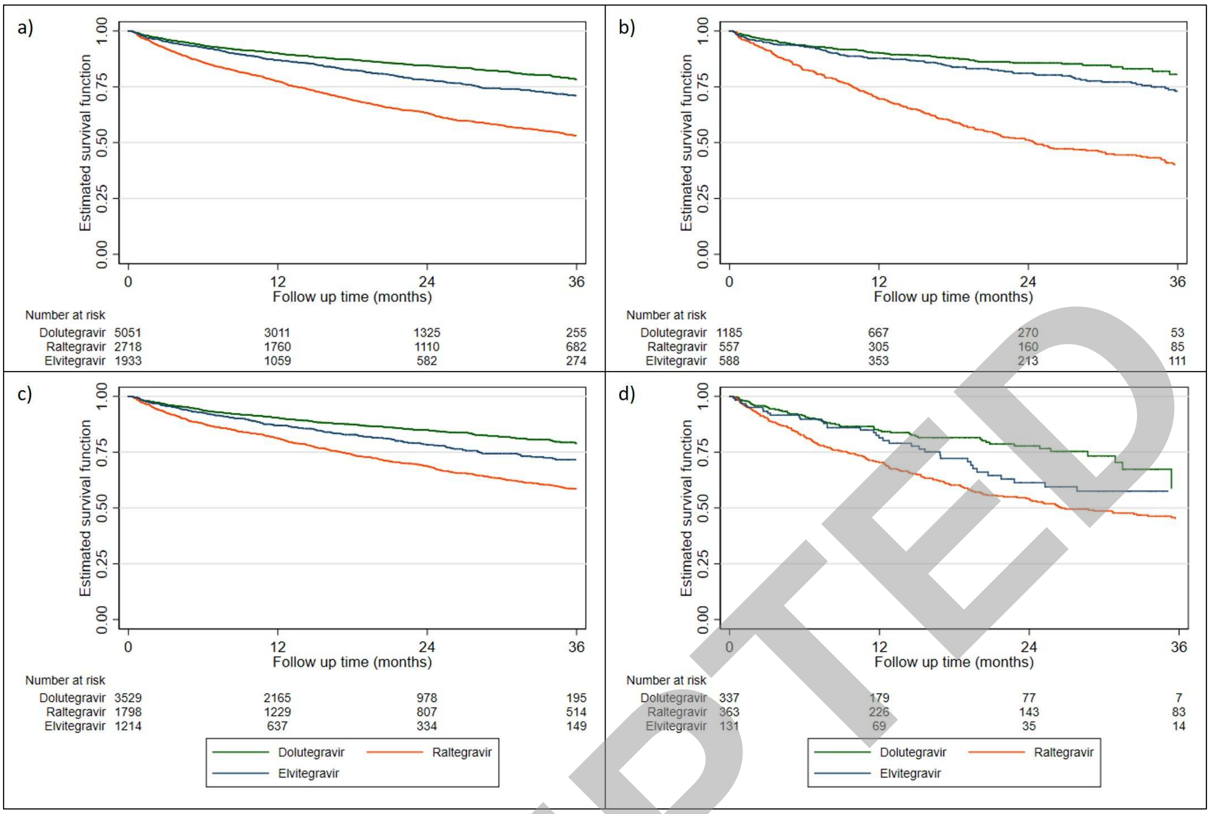
Hepatitis B†	No	Yes	1.60	(1.19, 2.17)	0.002	1.68	(1.30, 2.19)	<0.001
Hypertension†	No	Yes	0.90	(0.76, 1.07)	0.24	0.85	(0.73, 0.98)	0.03
Diabetes†	No	Yes	1.20	(0.95, 1.51)	0.13	1.07	(0.85, 1.34)	0.58
Prior AIDS†	No	Yes	1.29	(1.09, 1.52)	0.003	0.71	(0.60, 0.84)	<0.001
Prior NADM†	No	Yes	1.23	(0.89, 1.70)	0.21	0.67	(0.47, 0.97)	0.03
Prior ESLD†	No	Yes	1.38	(0.74, 2.59)	0.31	0.54	(0.21, 1.42)	0.21
Prior CVD†	No	Yes	2.34	(1.69, 3.24)	<0.001	1.00	(0.70, 1.44)	0.99
Prior fracture†	No	Yes	0.60	(0.43, 0.83)	0.002	1.06	(0.80, 1.40)	0.67
Prior CKD†	No	Yes	1.32	(0.94, 1.83)	0.11	0.76	(0.52, 1.10)	0.14

Abbreviations: RR-risk ratio; CI- confidence interval; INSTI-integrase inhibitor; ART-antiretroviral treatment; MSM-men who have sex with men; IDU-intravenous drug user; VL-viral load; NADM-non-AIDS defining malignancies; ESLD-end stage liver disease; CVD-cardiovascular disease; CKD-chronic kidney disease

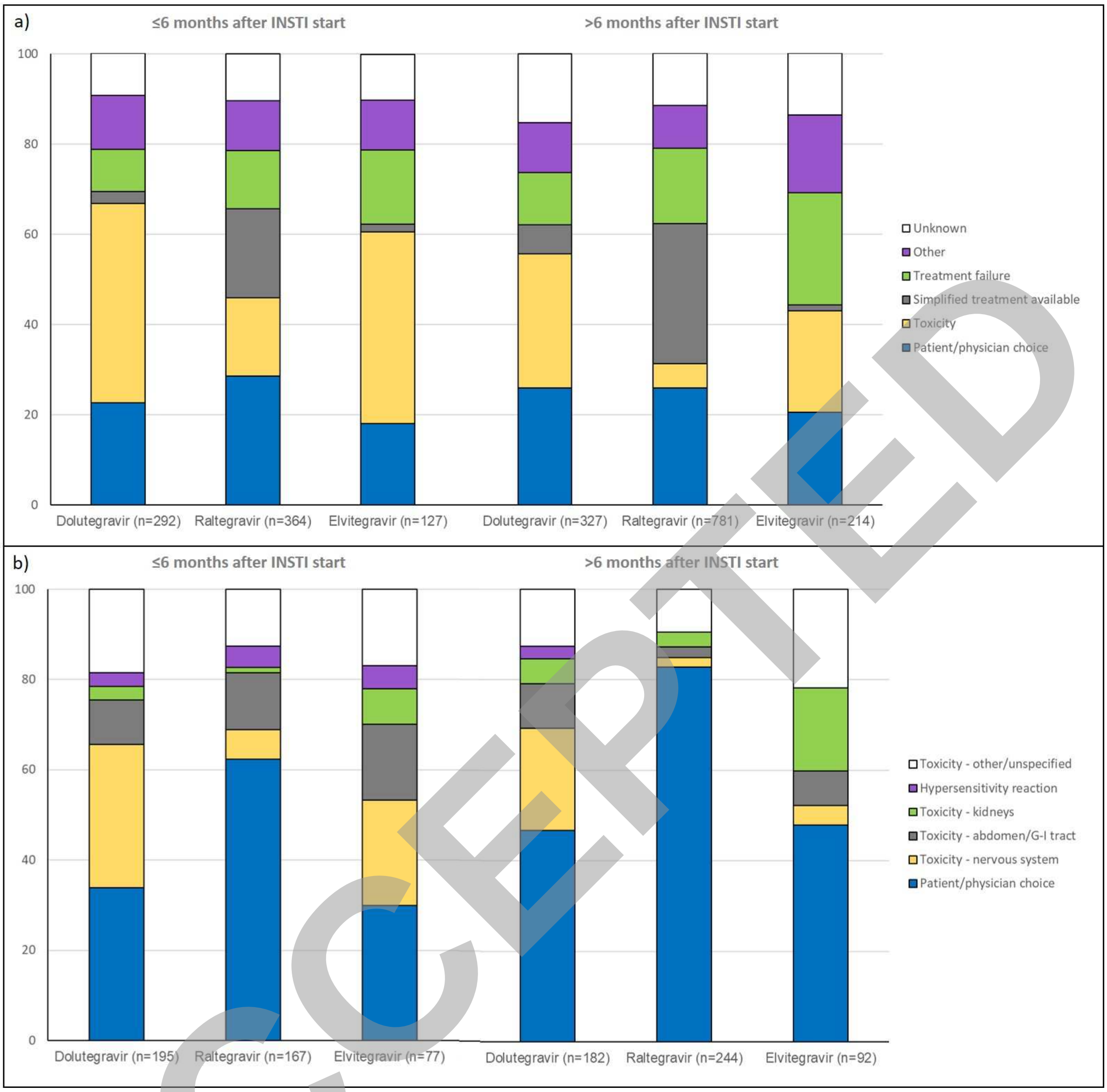
*Results from a multivariable, multinomial logistic regression; all variables were fitted in the model simultaneously

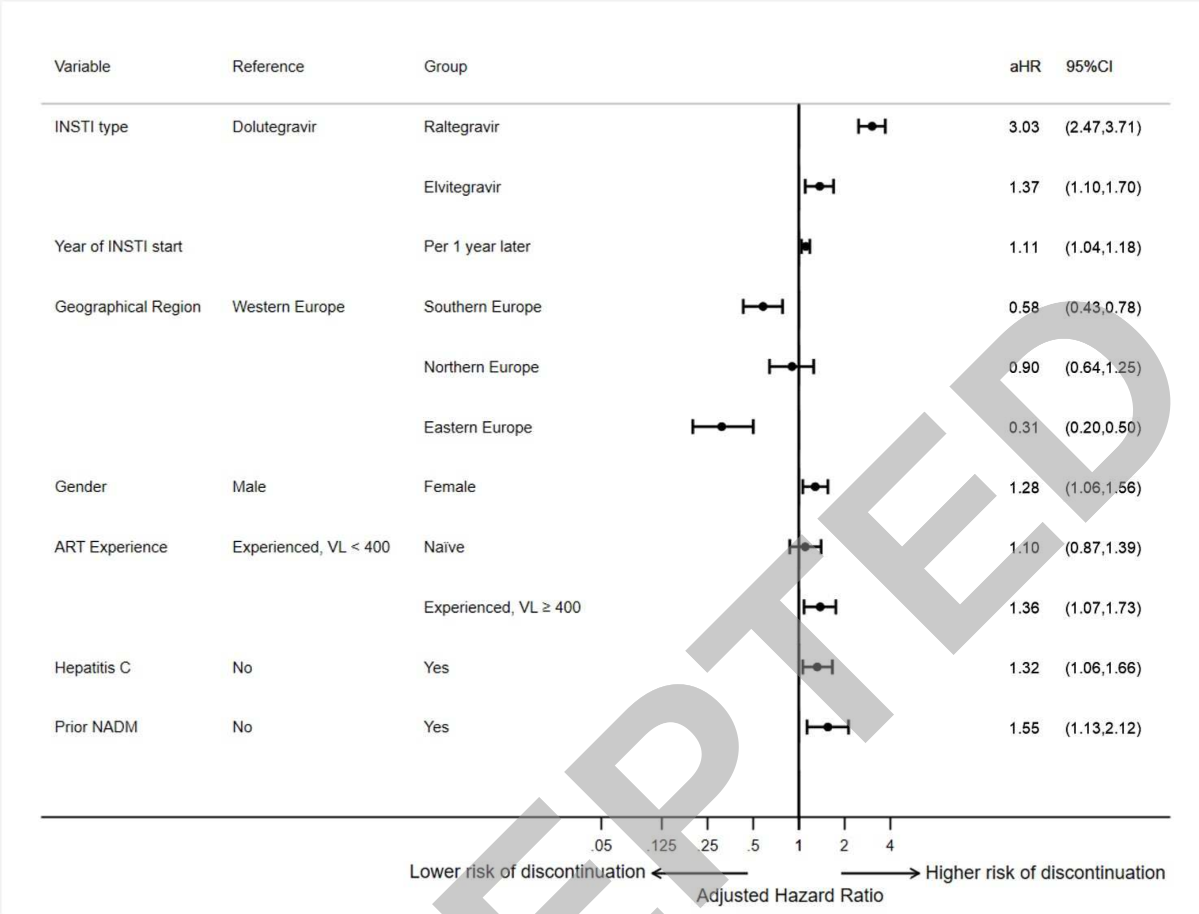
[1]Due to low counts, Australia is grouped with Northern Europe and Eastern Central Europe is grouped with Eastern Europe.

[†]Missing data fitted as an unknown category (data not shown)



a)
Estimated survival function
0.00
0.25
0.50
0.75
1.00
0
12
24
36
Follow up time (months)
Number at risk
Dolutegravir 5051 3011 1325 255
Raltegravir 2718 1760 1110 682
Elvitegravir 1933 1059 582 274
b)
Estimated survival function
0.00
0.25
0.50
0.75
1.00
0
12
24
36
Follow up time (months)
Number at risk
Dolutegravir 1185 667 270 53
Raltegravir 557 305 160 85
Elvitegravir 588 353 213 111
c)
Estimated survival function
0.00
0.25
0.50
0.75
1.00
0
12
24
36
Follow up time (months)
Number at risk
Dolutegravir 3529 2165 978 195
Raltegravir 1798 1229 807 514
Elvitegravir 1214 637 334 149
Dolutegravir
Raltegravir
Elvitegravir
d)
Estimated survival function
0.00
0.25
0.50
0.75
1.00
0
12
24
36
Follow up time (months)
Number at risk
Dolutegravir 337 179 77 7
Raltegravir 363 226 143 83
Elvitegravir 131 69 35 14
Dolutegravir
Raltegravir
Elvitegravir


a)
≤6 months after INSTI start
>6 months after INSTI start
100
80
60
40
20
0
Dolutegravir (n=292)
Raltegravir (n=364)
Elvitegravir (n=127)
Dolutegravir (n=327)
Raltegravir (n=781)
Elvitegravir (n=214)
Unknown
Other
Treatment failure
Simplified treatment available
Toxicity
Patient/physician choice
b)
≤6 months after INSTI start
>6 months after INSTI start
Dolutegravir (n=195)
Raltegravir (n=167)
Elvitegravir (n=77)
Dolutegravir (n=182)
Raltegravir (n=244)
Elvitegravir (n=92)
Toxicity - other/unspecified
Hypersensitivity reaction
Toxicity - kidneys
Toxicity - abdomen/G-I tract
Toxicity - nervous system
Patient/physician choice


Variable
Reference
Group
aHR
95%CI
INSTI type
Dolutegravir
Raltegravir
3.03
(2.47,3.71)
Elvitegravir
1.37
(1.10,1.70)
Year of INSTI start
Per 1 year later
1.11
(1.04,1.18)
Geographical Region
Western Europe
Southern Europe
0.58
(0.43,0.78)
Northern Europe
0.90
(0.64,1.25)
Eastern Europe
0.31
(0.20,0.50)
Gender
Male
Female
1.28
(1.06,1.56)
ART Experience
Experienced, VL < 400
Naïve
1.10
(0.87,1.39)
Experienced, VL ≥ 400
1.36
(1.07,1.73)
Hepatitis C
No
Yes
1.32
(1.06,1.66)
Prior NADM
No
Yes
1.55
(1.13,2.12)
.05
.125
.25
.5
1
2
4
Lower risk of discontinuation
Higher risk of discontinuation
Adjusted Hazard Ratio